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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
SHUKLA, R	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/101,423	Applicant(s) RUDLAND ET AL.	
	Examiner Ram Shukla	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,11,15-19,23 and 29* is/are pending in the application.

4a) Of the above claim(s) *8-10,12-14,20-22 and 24-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,11,15-19,23 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of the invention of group I in Paper No. 8 filed 12-6-99 is acknowledged. The traversal is on the ground(s) that (i) there is commonality of purpose in the claimed subject matter; (ii) even though DNA sequences are different they correspond to a singly inventive concept and (iii) different sequences contain certain common elements. This is not found persuasive because the search of a DNA sequence is based on the sequence, which is different for all the claimed sequences. Furthermore, the utility of each DNA sequence would be distinct, and a method using one DNA will not be the same as a method using another DNA. Furthermore, the regulatory sequences may be part of totally unrelated genes, which have different pattern of expression. There is no evidence of record to indicate that the DNA sequences disclosed in different SEQ ID NOs. 1-6 are part of the same gene or their mechanism of gene regulation is same or they are related. In fact, specification states that the six DNA bear little relationship to one another (see line 10-12 from bottom of page 16).

The requirement is still deemed proper and is therefore made FINAL.

2. Applicants have indicated in their response that in case the restriction is made final, they would like the sequence of claim 11 to be substituted for claim 8. They further indicate that accordingly group I would contain claims 1-7, 11, 15-19, 23, and 29. For customer service and to expedite prosecution and as requested by the Applicants, claims 1-7, 11, 15-19, 23, and 29 pertaining to SEQ ID NO 4 would be examined in the instant office action.

3. Claims 8-10, 12-14, 20-22, and 24-28 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8.

4. Claims 1-7, 11, 15-19, 23, and 29 pertaining to SEQ ID NO 4 are under consideration.

5. Compliance With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2) (for example claims 6 and 11 and pages 13-16 of the specification).

It is noted that while a CRF and paper copy of sequence listing has been submitted, the sequences in the specification and claims are not identified by sequence identifiers, as required by 37 C.F.R. § 1.821(a)(2) (d).

Applicants are required to correct the specification and claims to conform to 37 C.F.R. § 1.821(a)(1) and (a)(2) (see MPEP 2422).

Specification

6. The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

The following order or arrangement is preferred in framing the specification and, except for the reference to "Microfiche Appendix" and the drawings, each of the lettered items should appear in upper case, without underlining or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) Title of the Invention.
(b) Cross-References to Related Applications.
(c) Statement Regarding Federally Sponsored Research or Development.
(d) Reference to a "Microfiche Appendix" (see 37 CFR 1.96).
(e) Background of the Invention.
    1. Field of the Invention.
    2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) Brief Summary of the Invention.
(g) Brief Description of the Several Views of the Drawing(s).
(h) Detailed Description of the Invention.
(i) Claim or Claims (commencing on a separate sheet).
(j) Abstract of the Disclosure (commencing on a separate sheet).
(k) Drawings.
(l) Sequence Listing (see 37 CFR 1.821-1.825).

7. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 17 and 29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claimed invention is directed to a medicament to target a regulatory DNA that induces metastasis wherein the DNA is 1-6 kb in length obtained from a metastasis cancer cell. Claim 17 limits that the regulatory DNA is SEQ ID NO 4. The specification as filed in not enabling for the claimed invention because the invention as filed does not provide any guidance, working example or prophetic example as to how the claimed invention would have been made and used by an artisan of skill without undue experimentation.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue". Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The specification is not enabling for the claimed invention because the specification does not provide any guidance as to how the claimed medicament would have been prepared, what disease would have been treated, what doses would have been administered, and whether treatment of any disease would have been resulted after the administration of the claimed medicament . It is noted that the only description provided by the specification is on page 19 (last 6 lines) and page 20, which indicates that oligonucleotides could be used for blocking the expression the function of a regulatory DNA in a cancer. The specification does not provide as to what cancer would have been treated by the claimed invention, what part of the DNA would have been targeted, what would be the structure of the antisense or ribozyme, what would be the method of administration of the medicament and what doses would have been used. Additionally, the specification does not provide any guidance as to what method would have been used to assess whether the treatment was effective in treating the cancer.

Additionally, it is noted that the art of antisense therapy is highly unpredictable in general. Additionally, for using this therapeutic approach, before an artisan can actually apply this method to a patient, one would have to standardize, study, and determine several factors. Sherman (Annals of NY Acad. Sci. 616:201-204, 1990), in their review, list some of the parameters and potential problems associated with antisense therapy. For example, antisense sequences directed against different regions of a target nucleic acid would be differentially active, such as the antisense sequences that hybridize with the 5' end of a mRNA would have different levels of effects on the expression of the targeted gene, compared to sequences targeting the internal regions of the mRNA because they would target different steps of gene expression. These factors will be further compounded by the fact that base compositions as well as tertiary structure of the target sequence will determine the accessibility of the target sequence to the antisense sequence. Additionally, in order to be maximally effective, the antisense molecules must reach their respective intracellular target in an intact state. Sherman states " it is likely that in patients there will be a series of impediments to achieving this end." In a more recent appraisal of the state of the antisense therapeutic art, Holt (Mol Med Today 2:184-185, 1996) states, "meanwhile, back at the research bench, the development of clinical applications for this methodology continues to proceed at a slower pace than the improvements in nucleotide chemistry and pharmacology. A major problem has been the identification of appropriate gene targets and good or even reasonable disease model to test the oligonucleotide based strategies."

In another review, Rojanasakul (Advanced Drug Delivery Reviews 18:115-131, 1996) analyzed the issue: can antisense work in living system and discusses issues such as, how can antisense oligonucleotides be targeted to diseases cells, sparing normal cells and many instances one would see more effect on gene expression with a control oligo than the target oligo. Another issue is their degradation and effects of the degradation products on gene expression and cellular metabolism. Rojanasakul further reiterates that art recognized fact that the in vitro effects of oligos may not necessarily reflect their in vivo effects. Furthermore, nonspecific effects of oligos, eg. In case of antisense oligos targeting rel A transcription factor induced thrombocytopenia and renal failure, have also been reported (see page 118).

In conclusion, the art of antisense therapy is highly unpredictable and the specification has filed has failed to provide sufficient guidance as to how would an artisan have dealt with the art recognized issues such as those listed above and therefore it would have required undue experimentation for an artisan to have successfully practiced the claimed invention with a reasonable expectation of success.

10. Claims 1-5, 18, and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed method wherein human DNA is transfected into rat mammary epithelial cells, Rama 37, and transformed Rama 37 cells are injected into rats, does not reasonably provide enablement for other claimed embodiments. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

It is noted that the claimed invention in the currently presented format would encompass transformation of any and all cells with a human DNA from malignant tissue and injecting the cells in any syngeneic animal and said injection would result in metastasis formation in the animal including humans and human cells. However, the specification does not provide sufficient guidance and working examples as to how an artisan of skill would have made and used the claimed invention commensurate in scope of the claims.

It is noted that the first requisite of the method is that in step (i) transfection of a DNA from a metastatic DNA would result in the transformation of the cell such that it would produce a metastasis when injected in an animal, however, the mechanisms of the development of

metastasis or transformation of a cell into a metastasizing cell are not fully understood. Furthermore, the claimed method would require a transcription regulatory element (provided by the DNA fragments) to change the expression pattern of a gene whose expression product will result in the transformation of a cell. Again, there is nothing on record to indicate that any DNA fragment from any malignant cell when introduced in a cell will result in cell transformation. The specification does not describe any data as to what percent of the DNA fragments produced transformed the DNA, what parameters would an artisan have used to fragment DNA so as to obtain a size that would be sufficient to transform a cell. Yet another requirement for practicing the claimed method would be changing any cell into a cell that would produce a benign, non-metastasizing tumors when injected into a syngeneic animal. The specification does not provide any guidance as to how an artisan of skill have converted or transformed a normal cell or cell line in to a cell that would have produced benign, non-metastasizing tumors in an animal. Furthermore, the claimed method when given broadest interpretation would require that even a 50 kb DNA would have cell transforming activity, however, it is not clear as to how an artisan of skill would have introduced such a large size DNA in a cell and whether the transformation was due to a regulatory element or a gene being expressed from the DNA transfected in the cells.

As noted above, the method will only work when the DNA being transfected in a cell results in the transformation of the cell, however, the state of the art of cell transformation and cancer development is still not well understood. Ilyas et al (Ilyas M et al. Eur J of Cancer 35:1986-2002, 1999) noted that normal cells become malignant as a result of somatic evolution and metastasis of tumor cells to a new environment may drive evolution of the metastatic deposits in a different direction than the primary tumor and for full understanding of the process would include all the genetic pathways and genes involved would need to be identified (see the future perspectives on page 1997). In other words, the mechanism of tumor development and metastasis development is a complex phenomenon and the field is unpredictable. In conclusion, an artisan would have required extensive experimentation of trial and errors to first change a cell into a transformed cell that would only produce nonmetastatic tumors when injected in an animal, before the claimed method could be practiced and such experimentation would have been undue because the specification does not provide sufficient guidance as to how an artisan would have changed a normal cell into a cell that produces nonmetastatic tumors and whether any DNA fragment from a malignant cell when introduced in such a cell would have transformed the cell into a metastasis producing cells.

Therefore, the specification as filed in not enabling for making and using the claimed invention commensurate with the scope of the claims and limiting the scope of the claimed invention to a method wherein human DNA is transfected into rat mammary epithelial cells, Rama 37, and transformed Rama 37 cells are injected into rats, is proper.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 6,11, and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 is indefinite because it is unclear as whether the claimed DNA is the entire sequence of SEQ ID NO 4 or whether it is directed to fragments of SEQ ID NO 4.

Claim 11 is also vague and indefinite because it is unclear as to what is the term "C9" supposed to represent in the claimed invention.

Claim 6 is vague and indefinite because it is unclear as to which of the oligonucleotides, the term "an oligonucleotide sequence" is intended to be represent, since two oligonucleotides are recited in the claim.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1-5, 7, 15, 18, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Davies et al (Davies BR et al. Cancer Research 54:2785-2793, 1994).

Davies et al teach a method of induction of metastasis by transfecting a metastasis associated DNA in rat mammary epithelial cells and administering the transfected cells in a syngeneic rat. Without transfection with the DNA, these rat mammary epithelial cells, Rama 37, produce nonmetastasizing, adenomatous tumors in syngeneic rats) (see the entire article). As noted in the methods section, the size of the fragments ranged from 300 bp to 23 kb (see

second paragraph from bottom in column 2 on page 2785). Davies et al further teach oligonucleotides that can be used for identifying the human DNAs (tags and probes) (see figure 1). Figure 5 shows the difference between the DNA hybridization pattern of a metastatic DNA contain cell and a cell that does not contain metastasis-inducing DNA. As seen in this figure, the size of the DNA fragments ranges from less than 2 kb to 10 kb (compare the band pattern in lane 3 with other lanes).

Accordingly, the invention of claims 1-5, 7, 15, 18, and 19 is anticipated by Davies et al.

15. The primer disclosed in claim 6 and the DNA sequence of SEQ ID NO 4 are free of prior art on record.

Applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c). For instruction, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Kay Pinkney whose telephone number is (703) 305-3553.

Ram R. Shukla, Ph.D.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER